Traditional Chinese Medicine 中医学, 2025, 14(12), 5389-5398
Published Online December 2025 in Hans. https://www.hanspub.org/journal/tcm
https://doi.org/10.12677/tcm.2025.1412775

中草药单体调节氧化磷酸化干预DKD的分子机制

尹程倩，王立范*

黑龙江省中医药科学院，黑龙江 哈尔滨

收稿日期：2025年10月28日；录用日期：2025年12月1日；发布日期：2025年12月11日

摘　要

糖尿病肾病(DKD)的病理进展与线粒体氧化磷酸化(OXPHOS)功能障碍以及氧化应激密切相关，但目前缺乏直接靶向该通路的有效治疗药物。本研究系统性地评估了多种中药单体调节线粒体OXPHOS通路、缓解氧化应激的分子机制及其临床转化潜力。我们发现，不同类型的中药单体通过靶向调控线粒体电子传递链(ETC)的特定复合物来发挥肾脏保护作用。例如，多酚类化合物主要激活SIRT1/PGC-1α信号轴，增强氧化磷酸化活性；苷类化合物通过Nrf2/TFAM通路促进线粒体生物合成并恢复氧化磷酸化。这些发现揭示了不同类型中药单体在多层次、多靶点调控线粒体OXPHOS系统中的巨大潜力，为开发新型DKD治疗药物提供了坚实的理论框架和多靶点选择。

关键词

糖尿病肾病(DKD)，氧化磷酸化(OXPHOS)，足细胞损伤，中草药单体，氧化应激

Molecular Mechanisms of Monomer Compounds from Chinese Herbal Medicine in Regulating Oxidative Phosphorylation for Intervention in Diabetic Kidney Disease

Chengqian Yin, Lifan Wang*

Heilongjiang Academy of Chinese Medicine Sciences, Harbin Heilongjiang

Received: October 28, 2025; accepted: December 1, 2025; published: December 11, 2025

*通讯作者。

文章引用: 尹程倩, 王立范. 中草药单体调节氧化磷酸化干预 DKD 的分子机制[J]. 中医学, 2025, 14(12): 5389-5398.
DOI: 10.12677/tcm.2025.1412775

Abstract

The pathological progression of diabetic kidney disease (DKD) is closely associated with mitochondrial oxidative phosphorylation (OXPHOS) dysfunction and oxidative stress, yet effective therapeutic agents directly targeting this pathway remain scarce. This study systematically evaluated the molecular mechanisms by which multiple Chinese herbal monomers modulate the mitochondrial OXPHOS pathway and alleviate oxidative stress, alongside their clinical translational potential. We discovered that distinct classes of TCM monomers exert renal protective effects by targeting specific complexes within the mitochondrial electron transport chain (ETC). For instance, polyphenolic compounds primarily activate the SIRT1/PGC-1α signaling axis to enhance oxidative phosphorylation activity, whilst glycosides promote mitochondrial biogenesis and restore oxidative phosphorylation via the Nrf2/TFAM pathway. These findings reveal the substantial potential of diverse TCM monomers to regulate the mitochondrial OXPHOS system through multi-level, multi-target mechanisms, providing a robust theoretical framework and multi-target options for developing novel DKD therapeutics.

Keywords

Diabetic Kidney Disease (DKD), Oxidative Phosphorylation (OXPHOS), Podocyte Injury, Herbal Monomers, Oxidative Stress

1. 介绍

糖尿病肾病(Diabetic Kidney Disease, DKD)是糖尿病主要微血管并发症，累及约 40%的长期糖尿病患者，其病理进程呈现阶段性演变特征[1] [2]。疾病初期表现为肾小球高滤过与微量白蛋白尿，随病程进展出现大量蛋白尿，最终导致终末期肾病(End-Stage Renal Disease, ESRD)并需肾脏替代治疗[3] [4]。足细胞损伤是 DKD 核心病理机制[5]-[7]，且其损伤程度已成为评估疾病预后的独立危险因素[8] [9]。该病理过程涉及以下机制：高血糖介导的线粒体氧化应激、炎性小体激活触发的慢性炎症级联反应、肾小球内高血压诱导的血流动力学紊乱，以及线粒体功能障碍[10]-[12]。其中，线粒体氧化应激与氧化磷酸化之间存在密切的关系，这种关系不仅体现在氧化磷酸化过程中活性氧(Reactive Oxygen Species, ROS)的产生，还涉及氧化应激对线粒体功能和代谢的调控作用。

线粒体氧化磷酸化(OXPHOS)系统构成细胞能量代谢的核心枢纽，其通过电子传递链(Electron Transport Chain, ETC)的四种蛋白复合物(I~IV)与 ATP 合成酶(复合物 V)协同作用，实现氧化还原反应与 ATP 合成的能量耦合[13]。ETC 复合物 I (NADH 脱氢酶)作为电子传递的初始位点，同时是 ROS 生成的主要来源[14]。研究表明，复合物 I 通过构象变化(活性状态→休眠状态转换)动态调节 ROS 水平。复合物 III (泛醌－细胞色素 c 还原酶)同样参与 ROS 生成，其功能抑制可显著增强线粒体 ROS 产生[15] [16]。在抗氧化防御系统受损的条件下，过量蓄积的 ROS 作为应激介质，诱发氧化应激状态[17]。因此，靶向调节 OXPHOS 系统关键组分(尤其复合物 I~IV)的活性状态，成为干预 DKD 氧化应激损伤的新兴治疗策略。

尽管线粒体 OXPHOS 系统的重要性日益凸显，但目前针对其进行精准调控以治疗 DKD 的药物研究仍处于起步阶段。现有研究大多集中于泛泛的抗氧化或抗炎策略，未能深入剖析如何通过调控特定的线

粒体复合物来恢复其功能。现有研究证实多酚类、皂苷类及生物碱类中草药单体在 DKD 治疗中具有显著药理活性[18]-[21]，其通过调节氧化磷酸化(OXPHOS)通路发挥治疗作用的分子机制尚未完全阐明。

本文将详细阐述这些中药单体如何通过精准调控线粒体 OXPHOS 系统来缓解 DKD 的病理损伤。这项研究为未来基于线粒体 OXPHOS 功能调控的 DKD 精准治疗和药物开发提供了重要的科学依据。

2. 中草药单体通过调节 OXPHOS 干预 DKD

中草药具有多种活性成分，多酚类、皂苷类及生物碱类中草药单体可特异性靶向线粒体分子元件，选择性调控 OXPHOS 代谢通路，为干预 DKD 的线粒体功能障碍提供分子基础。

2.1. 多酚

多酚类化合物作为中草药的代表性活性组分，其结构多样性及多重生物活性已得到充分表征。该类化合物的分子结构特征为芳香环多羟基取代，主要包括黄酮类、单宁类与木脂素等亚型[22]。作为植物的次级代谢产物，天然多酚类化合物具有抗氧化、抗炎及调节自噬等多种生物活性[23] [24]。

2.1.1. 白藜芦醇

白藜芦醇(Resveratrol)是一种天然多酚类化合物，存在于虎杖(*Polygonum cuspidatum*)和莎草属(*Cyperaceae*，如 *C. rotundus*)等传统中草药中，具有多种生物学效应[25]。该化合物具有显著的抗氧化能力，可通过清除自由基和抑制脂质过氧化来保护细胞免受氧化应激损伤[26]。此外，白藜芦醇还可改善胰岛素敏感性并调节糖代谢，对糖尿病具有潜在的预防和治疗作用[27]。

研究显示，白藜芦醇通过激活 AMPK，抑制 mTOR 下游效应物 S6 激酶和 4E-BP1 的磷酸化，从而减轻肾脏氧化应激和纤维化[28]。此外，白藜芦醇通过激活 SIRT1 及其下游靶点发挥关键作用。这包括激活 SIRT1/FOXO3a 信号轴，介导线粒体保护效应，改善高糖诱导的足细胞氧化应激损伤和凋亡[29]。

PGC-1α (过氧化物酶体增殖物激活受体 γ 辅激活因子 1α)是调控线粒体生物合成和功能的核心转录共激活因子[30]。SIRT1 通过去乙酰化激活 PGC-1α，增强其转录活性[31]。进而提升电子传递链复合物 I 与 III 的活性，稳定线粒体膜电位；抑制细胞色素 C (Cytochrome c)及促凋亡蛋白从线粒体向胞质的异常转位[32]。鉴于复合物 I 和 III 是生理与病理状态下 ROS 生成的关键位点[15]，RES 通过增强二者活性降低 ROS 水平，进而减轻高糖诱导的氧化应激与蛋白尿[32]。综上，白藜芦醇主要通过激活 SIRT1/PGC-1α 信号轴，靶向增强 OXPHOS 通路(特别是复合物 I 和 III)的功能，抑制线粒体 ROS 爆发，从而治疗 DKD 引起的足细胞损伤[33]。

2.2. Glucosides

苷类天然产物是指由糖基(如葡萄糖、果糖等)与非糖部分(如黄酮、皂苷、生物碱等)通过糖苷键连接而成的化合物。根据苷元的结构和来源，苷类天然产物可以分为多种类型，如黄酮苷、皂苷、氰苷、核苷等[34] [35]。

2.2.1. 红景天苷

红景天苷(Salidroside)是传统中草药红景天的主要活性成分(属黄酮苷类化合物) [36]，在多种肾脏疾病模型中表现出显著的保护作用[37] [38]。例如，红景天苷通过抑制 TLR4/NF-κB 和 MAPK 信号通路，减少炎症因子释放并抑制上皮－间质转化(EMT)，从而减轻肾间质纤维化及细胞外基质(ECM)沉积，最终改善肾功能损伤[39]。红景天苷在 SAMP8 小鼠模型中通过调节铁代谢并抑制铁死亡相关蛋白(如 GPX4、SLC7A11)的表达，显著抑制肾纤维化进程[40]。

在 db/db 糖尿病模型中，红景天苷可显著降低尿白蛋白排泄率并改善肾功能损伤[41] [42]，同时抑制

高糖诱导的足细胞凋亡[43]。红景天苷还可通过激活 SIRT1/Nrf2 信号通路上调 SIRT1 和 Nrf2 蛋白表达，进而激活 Nrf2 调控的抗氧化酶(如 HO-1 和 NQO1)，显著降低脂多糖诱导的肾组织 ROS 水平，从而增强足细胞抗氧化能力并减轻氧化应激损伤[44]。

AMPK 的激活可以促进线粒体生物发生，而线粒体生物发生通常与复合物 I 的活性增强有关[45]。红景天苷通过激活 AMPK/SIRT1 通路，改善线粒体功能，从而影响复合物 I 的活性。红景天苷还通过激活 SIRT1/PGC-1α 通路维持足细胞足突结构完整性，并修复链脲佐菌素(STZ)诱导的线粒体功能障碍，尤其可恢复呼吸链复合物 IV (细胞色素 c 氧化酶)活性[46]。与白藜芦醇激活 SIRT1/PGC-1α 通路不同的是，红景天苷则主要通过抑制 β-catenin 信号通路来减轻肾小球损伤和蛋白尿。该作用直接提升 OXPHOS 效率，减少线粒体 ROS 蓄积，从而维持足细胞足突结构完整性。其治疗 DKD 的多靶点机制体现为：修复复合物 IV 功能以优化 OXPHOS 效率；降低线粒体 ROS 蓄积以缓解氧化应激；维持足细胞线粒体稳态以延缓疾病进展。红景天苷主要通过激活 SIRT1/Nrf2 通路增强抗氧化能力，同时激活 SIRT1/PGC-1α 通路并修复呼吸链复合物 IV 活性。

2.2.2. 黄芪甲苷-IV

黄芪甲苷 IV (AS-IV)是一种从黄芪(*Astragalus membranaceus*)中提取的天然三萜皂苷类化合物，具有广泛的药理活性和临床应用价值[47] [48]。它在传统中医中被广泛使用，用于治疗多种疾病，包括心血管疾病、肝病、肾病、神经退行性疾病等[49]-[51]。其对肾脏的保护作用在：黄芪甲苷 IV 通过抑制 NLRP3 炎症小体的激活和相关炎症反应，从而在 DKD、顺铂诱导的肾损伤[52]。AS-IV 通过抑制 NF-κB 介导的炎症基因表达，减少炎症因子如 TNF-α、MCP-1 和 ICAM-1 的血清水平，从而减轻 DKD 中的炎症反应[53]。黄芪甲苷 IVAS-IV 还可以通过调节钙离子通道(如 TRPC6)和钙离子浓度，抑制高葡萄糖或棕榈酸诱导的足细胞凋亡[54]。钙离子稳态的调节有助于维持细胞功能并减少氧化应激[54]。在 db/db 小鼠模型中，黄芪甲苷 IV 显著改善肾功能障碍与足细胞损伤，延缓 DKD 进展[55]。黄芪甲苷 IV 通过调节 Nrf2/ARE 信号通路，增强抗氧化能力，减少 ROS 的产生，从而保护足细胞免受高血糖诱导的氧化损伤[56] [57]。

黄芪甲苷 IV 可以通过激活 Nrf2/线粒体转录因子 A (TFAM)通路促进线粒体生物合成，恢复电子传递链复合物 I 活性，优化 OXPHOS 代谢效率；此过程通过维持线粒体稳态保障细胞能量供应，最终减轻高糖诱导的足细胞损伤[58]。黄芪甲苷 IV 主要通过 Nrf2/TFAM 通路，恢复复合物 I 活性，从而恢复 OXPHOS，减少 ROS，减轻氧化应激，改善 DKD。

2.2.3. 虎杖苷

虎杖苷(Polydatin, PD)系中药西洋参(*Panax quinquefolius* L.)根的主要生物活性成分，属白藜芦醇苷类化合物[59]。虎杖苷通过多种机制对肾脏提供保护作用，包括抗氧化、抗炎、抗凋亡、抗纤维化、抑制铁死亡等[60] [61]。虎杖苷也能够改善心磷脂水平，从而维持复合物 III 和 IV 的正常功能，从而改善氧化磷酸化过程[62]。Polydatin 可以通过减少脂质过氧化、提高电子传递链(ETC)活性和减少 ROS 水平来保护线粒体功能[63]，并且靶向抑制 HIF-1α/NOX4 信号通路，减轻氧化应激并修复足细胞结构，从而保护肾小球功能[64]。

研究表明，虎杖苷通过激活 SIRT3，能够改善足细胞的氧化应激状态，从而减轻高果糖诱导的足细胞损伤[64]。SIRT3 通过去乙酰化作用增强复合物 I 和 II 的活性，从而提高线粒体的 ATP 生成能力[65]。基于此，基于虎杖苷通过 SIRT3 改善足细胞氧化磷酸化功能障碍的假说，可通过实验验证该机制，以填补 PD 靶向 OXPHOS 治疗的机制空白。

2.2.4. 人参皂苷

人参皂苷 Rb1 是人参中的一种主要活性成分，属于原人参二醇皂苷类化合物[66]。研究表明，人参

皂苷 Rb1 可以通过抑制线粒体电子传递链、诱导细胞凋亡、抑制自噬等机制发挥抗癌作用[67]。人参皂苷 Rb1 可以抑制心肌细胞线粒体复合物 I 的活性，减少 ROS 的产生，从而保护细胞免受氧化应激的损害[68]。

GRb1 通过抑制 NF-κB、JNK 和 p38 信号通路，减轻 TNF-α 介导的炎症损伤[69]。在链脲佐菌素(STZ)诱导的 DKD 模型中，人参皂苷 Rb1 通过特异性抑制醛糖还原酶(AR)活性，下调线粒体细胞色素 c (Cyto c)的释放，从而恢复 OXPHOS 的代谢效率；此过程通过增强线粒体呼吸功能减少 ROS 的生成，最终减轻了氧化应激介导的肾组织损伤[70]。人参皂苷 Rb1 通过优化线粒体电子传递链功能，尤其通过精准调控复合物 I 活性，从而有效预防反向电子传递(RET)介导的 ROS 损伤[68]。上述作用协同提升 OXPHOS 代谢效率，增强线粒体呼吸功能并减少 ROS 累积，最终通过恢复 OXPHOS 稳态减轻足细胞氧化应激损伤。

2.3. 生物碱

小檗碱(Berberine, BBR)是中药黄连(*Coptis chinensis* Franch)的特征性异喹啉类生物碱，亦是其肾脏保护作用的关键活性成分[71]。多项研究证实，小檗碱具有抗炎[72]与抗糖尿病活性[73]，为 DKD 的干预提供药理学基础。在 DKD 动物模型中证实，小檗碱改善肾小球硬化及基底膜增厚等病理改变，并逆转尿蛋白排泄增加与肌酐清除率降低等肾功能异常[74]。

研究发现，小檗碱能够剂量依赖性地抑制线粒体呼吸链复合物 I (Complex I)的活性[75]；然而存在报道显示，在 db/db 小鼠和高糖处理的足细胞中，研究发现 DKD 病理状态本身会导致复合物 I、IV 和 V 的活性显著下降，而小檗碱治疗则能够恢复这些复合物的活性，从而重建线粒体能量稳态[76]-[78]。对于看似矛盾的现象，可能是由于：在 DKD 的高糖环境下，线粒体处于功能紊乱状态，上游复合物(特别是复合物 I)可能因底物过载而“过度活化”，产生大量活性氧(ROS)，这种氧化应激进而损伤了包括复合物 IV (细胞色素 c 氧化酶)和复合物 V (ATP 合酶)在内的整个呼吸链，导致其功能下降。小檗碱的作用并非直接抑制功能已受损的复合物 IV 和 V。相反，小檗碱通过特异性地抑制上游的复合物 I，起到了“减压阀”的作用[75]；减轻氧化应激：抑制复合物 I 减少了电子泄漏和 ROS 的产生，从而保护了下游的复合物 IV 和 V 免受进一步的氧化损伤。

3. 讨论

氧化应激作为 DKD 发病机制的核心环节，其根源在于线粒体 OXPHOS 代谢紊乱。本综述表明，中草药单体凭借多靶点调控特性，在纠正足细胞 OXPHOS 功能障碍及缓解氧化应激方面具有显著潜力。目前关于天然活性成分调控 OXPHOS 的研究还存在大量空白，可以在未来进一步深入探讨。多酚类天然产物通过 AMPK/SIRT1/PGC-1α 通路，提升 OXPHOS 效率，从而减少 ROS，减轻氧化应激。AMPK/SIRT1/PGC-1α 通路是一个在能量代谢、线粒体功能、抗氧化应激和细胞存活中起关键作用的信号通路，其在多种生理和病理过程中具有广泛的应用和研究价值。

4. 结论

现有研究证实，靶向 OXPHOS 代谢通路是中草药单体治疗 DKD 的关键机制。不同类别活性成分(多酚类、苷类、生物碱类)通过特异性信号轴(如 AMPK/SIRT1、Nrf2/TFAM)改善足细胞线粒体能量代谢，从而缓解氧化应激损伤。这种多靶点干预模式突显了中草药在调节复杂代谢网络中的独特优势，为其成为 DKD 治疗候选药物奠定了理论基础。当前研究仍面临双重瓶颈：第一、机制深度不足：单一靶点研究难以解析 OXPHOS 与炎症、内质网应激的交互网络；第二、临床转化滞后：临床前模型与人体病理存在代际差异。

突破路径需聚焦以下方向首先，可以利用动物和细胞实验，深度挖掘中草药单体作用于足细胞氧化磷酸化的具体机制。如：在特定疾病模型(如基因敲除或药物干预)中，同步进行转录组、蛋白质组、磷酸化蛋白质组和代谢组学分析。其次，创新临床试验：建立基于线粒体生物标志物(如尿液 mtDNA)的适应性试验设计。以及在人体肾脏组织标本探索中草药单体对于足细胞的作用，探索临床前模型与人体病理在氧化磷酸化方面的差异。

参考文献

[1] Liu, D., Chen, X., He, W., Lu, M., Li, Q., Zhang, S., *et al.* (2024) Update on the Pathogenesis, Diagnosis, and Treatment of Diabetic Tubulopathy. *Integrative Medicine in Nephrology and Andrology*, **11**, e23-00029. https://doi.org/10.1097/imna-d-23-00029

[2] Wang, N. and Zhang, C. (2024) Recent Advances in the Management of Diabetic Kidney Disease: Slowing Progression. *International Journal of Molecular Sciences*, **25**, Article 3086. https://doi.org/10.3390/ijms25063086

[3] Ma, L., Yan, M., Kong, X., Jiang, Y., Zhao, T., Zhao, H., *et al.* (2018) Association of *EPHX2* R287Q Polymorphism with Diabetic Nephropathy in Chinese Type 2 Diabetic Patients. *Journal of Diabetes Research*, **2018**, Article ID: 2786470. https://doi.org/10.1155/2018/2786470

[4] Di Pino, A., Scicali, R., Marchisello, S., Zanoli, L., Ferrara, V., Urbano, F., *et al.* (2021) High Glomerular Filtration Rate Is Associated with Impaired Arterial Stiffness and Subendocardial Viability Ratio in Prediabetic Subjects. *Nutrition, Metabolism and Cardiovascular Diseases*, **31**, 3393-3400. https://doi.org/10.1016/j.numecd.2021.08.030

[5] Ruan, Z., Liu, J., Liu, W. and Huang, W. (2024) Qufeng Tongluo Decoction May Alleviate Podocyte Injury Induced by High Glucose and Hydrogen Peroxide by Regulating Autophagy. *Integrative Medicine in Nephrology and Andrology*, **11**, e24-00023. https://doi.org/10.1097/imna-d-24-00023

[6] Yang, H., Sun, J., Sun, A., Wei, Y., Xie, W., Xie, P., *et al.* (2024) Podocyte Programmed Cell Death in Diabetic Kidney Disease: Molecular Mechanisms and Therapeutic Prospects. *Biomedicine & Pharmacotherapy*, **177**, Article 117140. https://doi.org/10.1016/j.biopha.2024.117140

[7] Chen, Y., Chen, M., Zhu, W., Zhang, Y., Liu, P. and Li, P. (2024) Morroniside Attenuates Podocytes Lipid Deposition in Diabetic Nephropathy: A Network Pharmacology, Molecular Docking and Experimental Validation Study. *International Immunopharmacology*, **138**, Article 112560. https://doi.org/10.1016/j.intimp.2024.112560

[8] Chen, D., Guo, Y. and Li, P. (2024) New Insights into a Novel Metabolic Biomarker and Therapeutic Target for Chronic Kidney Disease. *Integrative Medicine in Nephrology and Andrology*, **11**, e24-00019. https://doi.org/10.1097/imna-d-24-00019

[9] Mao, N., Tan, R., Wang, S., Wei, C., Shi, X., Fan, J., *et al.* (2016) Ginsenoside Rg1 Inhibits Angiotensin II-Induced Podocyte Autophagy via AMPK/mTOR/PI3K Pathway. *Cell Biology International*, **40**, 917-925. https://doi.org/10.1002/cbin.10634

[10] Jia, J., Tan, R., Xu, L., Wang, H., Li, J., Su, H., *et al.* (2024) Hederagenin Improves Renal Fibrosis in Diabetic Nephropathy by Regulating Smad3/NOX4/SLC7A11 Signaling-Mediated Tubular Cell Ferroptosis. *International Immunopharmacology*, **135**, Article 112303. https://doi.org/10.1016/j.intimp.2024.112303

[11] Wang, Y., Sui, Z., Wang, M. and Liu, P. (2023) Natural Products in Attenuating Renal Inflammation via Inhibiting the NLRP3 Inflammasome in Diabetic Kidney Disease. *Frontiers in Immunology*, **14**, Article ID: 1196016. https://doi.org/10.3389/fimmu.2023.1196016

[12] Mima, A., Nomura, A. and Yasuzawa, T. (2025) Update on the Pathophysiology and Treatment of Diabetic Kidney Disease: A Narrative Review. *Expert Review of Clinical Immunology*, **21**, 921-928. https://doi.org/10.1080/1744666x.2025.2521086

[13] Qin, C., Gong, S., Liang, T., Zhang, Z., Thomas, J., Deng, J., *et al.* (2024) HADHA Regulates Respiratory Complex Assembly and Couples FAO and OXPHOS. *Advanced Science*, **11**, e2405147. https://doi.org/10.1002/advs.202405147

[14] Qi, B., Song, L., Hu, L., Guo, D., Ren, G., Peng, T., *et al.* (2022) Cardiac-Specific Overexpression of Ndufs1 Ameliorates Cardiac Dysfunction after Myocardial Infarction by Alleviating Mitochondrial Dysfunction and Apoptosis. *Experimental & Molecular Medicine*, **54**, 946-960. https://doi.org/10.1038/s12276-022-00800-5

[15] Cacace, J., Luna-Marco, C., Hermo-Argibay, A., Pesantes-Somogyi, C., Hernández-López, O.A., Pelechá-Salvador, M., *et al.* (2025) Poor Glycaemic Control in Type 2 Diabetes Compromises Leukocyte Oxygen Consumption Rate, OXPHOS Complex Content and Neutrophil-Endothelial Interactions. *Redox Biology*, **81**, Article 103516. https://doi.org/10.1016/j.redox.2025.103516

[16] Bochkova, Z.V., Baizhumanov, A.A., Yusipovich, A.I., Morozova, K.I., Nikelshparg, E.I., Fedotova, A.A., *et al.* (2025)

The Flexible Chain: Regulation of Structure and Activity of ETC Complexes Defines Rate of ATP Synthesis and Sites of Superoxide Generation. *Biophysical Reviews*, **17**, 55-88. https://doi.org/10.1007/s12551-025-01270-5

[17] Li, Q. and Sheikh-Hamad, D. (2023) Megalin Facilitates the Regulation of Mitochondrial Function by Extracellular Cues. *Integrative Medicine in Nephrology and Andrology*, **10**, e00015. https://doi.org/10.1097/imna-d-23-00015

[18] Wang, J., Zhang, R., Wu, C., Wang, L., Liu, P. and Li, P. (2024) Exploring Potential Targets for Natural Product Therapy of DN: The Role of Sumoylation. *Frontiers in Pharmacology*, **15**, Article ID: 1432724. https://doi.org/10.3389/fphar.2024.1432724

[19] Zhang, R., Wang, J., Wu, C., Wang, L., Liu, P. and Li, P. (2025) Lipidomics-Based Natural Products for Chronic Kidney Disease Treatment. *Heliyon*, **11**, e41620. https://doi.org/10.1016/j.heliyon.2024.e41620

[20] Liu, P., Chen, Y., Xiao, J., Zhu, W., Yan, X. and Chen, M. (2022) Protective Effect of Natural Products in the Metabolic-Associated Kidney Diseases via Regulating Mitochondrial Dysfunction. *Frontiers in Pharmacology*, **13**, Article ID: 1093397. https://doi.org/10.3389/fphar.2022.1093397

[21] Ma, X., Ma, J., Leng, T., Yuan, Z., Hu, T., Liu, Q., *et al.* (2023) Advances in Oxidative Stress in Pathogenesis of Diabetic Kidney Disease and Efficacy of TCM Intervention. *Renal Failure*, **45**, Article ID: 2146512. https://doi.org/10.1080/0886022x.2022.2146512

[22] Mamun, A.A., Shao, C., Geng, P., Wang, S. and Xiao, J. (2024) Polyphenols Targeting NF-*κ*B Pathway in Neurological Disorders: What We Know So Far? *International Journal of Biological Sciences*, **20**, 1332-1355. https://doi.org/10.7150/ijbs.90982

[23] Aryal, D., Joshi, S., Thapa, N.K., Chaudhary, P., Basaula, S., Joshi, U., *et al.* (2024) Dietary Phenolic Compounds as Promising Therapeutic Agents for Diabetes and Its Complications: A Comprehensive Review. *Food Science & Nutrition*, **12**, 3025-3045. https://doi.org/10.1002/fsn3.3983

[24] Sun, M., Deng, Y., Cao, X., Xiao, L., Ding, Q., Luo, F., *et al.* (2022) Effects of Natural Polyphenols on Skin and Hair Health: A Review. *Molecules*, **27**, Article 7832. https://doi.org/10.3390/molecules27227832

[25] Gielecińska, A., Kciuk, M., Mujwar, S., Celik, I., Kołat, D., Kałuzińska-Kołat, Ż., *et al.* (2023) Substances of Natural Origin in Medicine: Plants vs. Cancer. *Cells*, **12**, Article 986. https://doi.org/10.3390/cells12070986

[26] Kaur, A., Tiwari, R., Tiwari, G. and Ramachandran, V. (2022) Resveratrol: A Vital Therapeutic Agent with Multiple Health Benefits. *Drug Research*, **72**, 5-17. https://doi.org/10.1055/a-1555-2919

[27] Kim, Y.J., *et al.* (2017) Recent Studies on Resveratrol and Its Biological and Pharmacological Activity. *EXCLI Journal*, **16**, 602-608.

[28] Gowd, V., Kang, Q., Wang, Q., Wang, Q., Chen, F. and Cheng, K. (2020) Resveratrol: Evidence for Its Nephroprotective Effect in Diabetic Nephropathy. *Advances in Nutrition*, **11**, 1555-1568. https://doi.org/10.1093/advances/nmaa075

[29] Woodman, K., Coles, C., Lamandé, S. and White, J. (2016) Nutraceuticals and Their Potential to Treat Duchenne Muscular Dystrophy: Separating the Credible from the Conjecture. *Nutrients*, **8**, Article 713. https://doi.org/10.3390/nu8110713

[30] Bu, X., Wu, D., Lu, X., Yang, L., Xu, X., Wang, J., *et al.* (2017) Role of SIRT1/PGC-1*α* in Mitochondrial Oxidative Stress in Autistic Spectrum Disorder. *Neuropsychiatric Disease and Treatment*, **13**, 1633-1645. https://doi.org/10.2147/ndt.s129081

[31] Gao, J., Liu, P., Shen, Z., Xu, K., Wu, C., Tian, F., *et al.* (2021) Morroniside Promotes PGC-1*α*-Mediated Cholesterol Efflux in Sodium Palmitate or High Glucose-Induced Mouse Renal Tubular Epithelial Cells. *BioMed Research International*, **2021**, Article ID: 9942152. https://doi.org/10.1155/2021/9942152

[32] Zhang, T., Chi, Y., Kang, Y., Lu, H., Niu, H., Liu, W., *et al.* (2019) Resveratrol Ameliorates Podocyte Damage in Diabetic Mice via SIRT1/PGC-1*α* Mediated Attenuation of Mitochondrial Oxidative Stress. *Journal of Cellular Physiology*, **234**, 5033-5043. https://doi.org/10.1002/jcp.27306

[33] Wu, S., Wang, L., Wang, F. and Zhang, J. (2024) Resveratrol Improved Mitochondrial Biogenesis by Activating Sirt1/PGC-1*α* Signal Pathway in Sap. *Scientific Reports*, **14**, Article No. 26216. https://doi.org/10.1038/s41598-024-76825-9

[34] Moses, T., Papadopoulou, K.K. and Osbourn, A. (2014) Metabolic and Functional Diversity of Saponins, Biosynthetic Intermediates and Semi-Synthetic Derivatives. *Critical Reviews in Biochemistry and Molecular Biology*, **49**, 439-462. https://doi.org/10.3109/10409238.2014.953628

[35] Yulvianti, M. and Zidorn, C. (2021) Chemical Diversity of Plant Cyanogenic Glycosides: An Overview of Reported Natural Products. *Molecules*, **26**, Article 719. https://doi.org/10.3390/molecules26030719

[36] Shikov, A.N., Kosman, V.M., Flissyuk, E.V., Smekhova, I.E., Elameen, A. and Pozharitskaya, O.N. (2020) Natural Deep Eutectic Solvents for the Extraction of Phenyletanes and Phenylpropanoids of Rhodiola Rosea L. *Molecules*, **25**, Article 1826. https://doi.org/10.3390/molecules25081826

[37] Huang, X., Xue, H., Ma, J., Zhang, Y., Zhang, J., Liu, Y., *et al.* (2019) Salidroside Ameliorates Adriamycin Nephropathy

in Mice by Inhibiting *β*-Catenin Activity. *Journal of Cellular and Molecular Medicine*, **23**, 4443-4453. https://doi.org/10.1111/jcmm.14340

[38] Lai, W., Wang, B., Huang, R., Zhang, C., Fu, P. and Ma, L. (2024) Ferroptosis in Organ Fibrosis: From Mechanisms to Therapeutic Medicines. *Journal of Translational Internal Medicine*, **12**, 22-34. https://doi.org/10.2478/jtim-2023-0137

[39] Li, R., Guo, Y., Zhang, Y., Zhang, X., Zhu, L. and Yan, T. (2019) Salidroside Ameliorates Renal Interstitial Fibrosis by Inhibiting the TLR4/NF-*κ*B and MAPK Signaling Pathways. *International Journal of Molecular Sciences*, **20**, Article 1103. https://doi.org/10.3390/ijms20051103

[40] Fan, H., Su, B., Le, J. and Zhu, J. (2022) Salidroside Protects Acute Kidney Injury in Septic Rats by Inhibiting Inflammation and Apoptosis. *Drug Design, Development and Therapy*, **16**, 899-907. https://doi.org/10.2147/dddt.s361972

[41] Wu, D., Yang, X., Zheng, T., Xing, S., Wang, J., Chi, J., *et al.* (2016) A Novel Mechanism of Action for Salidroside to Alleviate Diabetic Albuminuria: Effects on Albumin Transcytosis across Glomerular Endothelial Cells. *American Journal of Physiology-Endocrinology and Metabolism*, **310**, E225-E237. https://doi.org/10.1152/ajpendo.00391.2015

[42] Zhao, Q., Shi, J., Chen, S., Hao, D., Wan, S., Niu, H., *et al.* (2022) Salidroside Affects Gut Microbiota Structure in db/db Mice by Affecting Insulin, Blood Glucose and Body Weight. *Diabetes, Metabolic Syndrome and Obesity*: *Targets and Therapy*, **15**, 2619-2631. https://doi.org/10.2147/dmso.s372192

[43] Lu, H., Li, Y., Zhang, T., Liu, M., Chi, Y., Liu, S., *et al.* (2017) Salidroside Reduces High-Glucose-Induced Podocyte Apoptosis and Oxidative Stress via Upregulating Heme Oxygenase-1 (HO-1) Expression. *Medical Science Monitor*, **23**, 4067-4076. https://doi.org/10.12659/msm.902806

[44] Pan, J., Zhu, J., Li, L., Zhang, T. and Xu, Z. (2023) Salidroside Attenuates LPS-Induced Kidney Injury through Activation of SIRT1/NRF2 Pathway. *Human & Experimental Toxicology*, **42**, 1-9. https://doi.org/10.1177/09603271231169520

[45] Zhao, D., Sun, X., Lv, S., Sun, M., Guo, H., Zhai, Y., *et al.* (2019) Salidroside Attenuates Oxidized Low-Density Lipoprotein-Induced Endothelial Cell Injury via Promotion of the AMPK/SIRT1 Pathway. *International Journal of Molecular Medicine*, **43**, 2279-2290. https://doi.org/10.3892/ijmm.2019.4153

[46] Xue, H., Li, P., Luo, Y., Wu, C., Liu, Y., Qin, X., *et al.* (2019) Salidroside Stimulates the SIRT1/PGC-1*α* Axis and Ameliorates Diabetic Nephropathy in Mice. *Phytomedicine*, **54**, 240-247. https://doi.org/10.1016/j.phymed.2018.10.031

[47] Liang, Y., Chen, B., Liang, D., Quan, X., Gu, R., Meng, Z., *et al.* (2023) Pharmacological Effects of Astragaloside IV: A Review. *Molecules*, **28**, Article 6118. https://doi.org/10.3390/molecules28166118

[48] Qu, C., Tan, X., Hu, Q., Tang, J., Wang, Y., He, C., *et al.* (2024) A Systematic Review of Astragaloside IV Effects on Animal Models of Diabetes Mellitus and Its Complications. *Heliyon*, **10**, e26863. https://doi.org/10.1016/j.heliyon.2024.e26863

[49] Zhu, Y. and Lu, F. (2024) Astragaloside IV Inhibits Cell Viability and Glycolysis of Hepatocellular Carcinoma by Regulating KAT2A-Mediated Succinylation of PGAM1. *BMC Cancer*, **24**, Article No. 682. https://doi.org/10.1186/s12885-024-12438-9

[50] Li, L., Wang, Q., He, Y., Sun, L., Yang, Y. and Pang, X. (2022) Astragaloside IV Suppresses Migration and Invasion of TGF-*β*1-Induced Human Hepatoma HuH-7 Cells by Regulating NRF2/Ho-1 and TGF-B1/Smad3 Pathways. *Naunyn-Schmiedeberg's Archives of Pharmacology*, **395**, 397-405. https://doi.org/10.1007/s00210-021-02199-8

[51] Wan, J., Zhang, Z., Wu, C., Tian, S., Zang, Y., Jin, G., *et al.* (2023) Astragaloside IV Derivative HHQ16 Ameliorates Infarction-Induced Hypertrophy and Heart Failure through Degradation of LncRNA4012/9456. *Signal Transduction and Targeted Therapy*, **8**, Article No. 414. https://doi.org/10.1038/s41392-023-01660-9

[52] Wang, H., Zhuang, Z., Huang, Y., Zhuang, Z., Jin, Y., Ye, H., *et al.* (2020) Protective Effect and Possible Mechanisms of Astragaloside IV in Animal Models of Diabetic Nephropathy: A Preclinical Systematic Review and Meta-Analysis. *Frontiers in Pharmacology*, **11**, Article No. 988. https://doi.org/10.3389/fphar.2020.00988

[53] Li, L., Zhang, Y., Luo, Y., Meng, X., Pan, G., Zhang, H., *et al.* (2023) The Molecular Basis of the Anti-Inflammatory Property of Astragaloside IV for the Treatment of Diabetes and Its Complications. *Drug Design, Development and Therapy*, **17**, 771-790. https://doi.org/10.2147/dddt.s399423

[54] Zang, Y., Liu, S., Cao, A., Shan, X., Deng, W., Li, Z., *et al.* (2021) Astragaloside IV Inhibits Palmitic Acid-Induced Apoptosis through Regulation of Calcium Homeostasis in Mice Podocytes. *Molecular Biology Reports*, **48**, 1453-1464. https://doi.org/10.1007/s11033-021-06204-4

[55] Feng, H., Zhu, X., Tang, Y., Fu, S., Kong, B. and Liu, X. (2021) Astragaloside IV Ameliorates Diabetic Nephropathy in db/db Mice by Inhibiting NLRP3 Inflammasome-Mediated Inflammation. *International Journal of Molecular Medicine*, **48**, Article No. 164. https://doi.org/10.3892/ijmm.2021.4996

[56] Gui, D., Guo, Y., Wang, F., Liu, W., Chen, J., Chen, Y., *et al.* (2012) Astragaloside IV, a Novel Antioxidant, Prevents Glucose-Induced Podocyte Apoptosis *in Vitro* and *in Vivo*. *PLOS ONE*, **7**, e39824. https://doi.org/10.1371/journal.pone.0039824

[57] Hu, Z., Zhou, Y., Gao, C., Liu, J., Pan, C. and Guo, J. (2024) Astragaloside IV Attenuates Podocyte Apoptosis via Regulating TXNIP/NLRP3/GSDMD Signaling Pathway in Diabetic Nephropathy. *Diabetology & Metabolic Syndrome*, **16**, Article No. 296. https://doi.org/10.1186/s13098-024-01546-y

[58] Shen, Q., Fang, J., Guo, H., Su, X., Zhu, B., Yao, X., *et al.* (2023) Astragaloside IV Attenuates Podocyte Apoptosis through Ameliorating Mitochondrial Dysfunction by Up-Regulated NRF2-ARE/TFAM Signaling in Diabetic Kidney Disease. *Free Radical Biology and Medicine*, **203**, 45-57. https://doi.org/10.1016/j.freeradbiomed.2023.03.022

[59] Jiang, K., Zhao, G., Deng, G., Wu, H., Yin, N., Chen, X., *et al.* (2017) Polydatin Ameliorates Staphylococcus Aureus-Induced Mastitis in Mice via Inhibiting TLR2-Mediated Activation of the P38 MAPK/NF-*κ*B Pathway. *Acta Pharmacologica Sinica*, **38**, 211-222. https://doi.org/10.1038/aps.2016.123

[60] Karami, A., Fakhri, S., Kooshki, L. and Khan, H. (2022) Polydatin: Pharmacological Mechanisms, Therapeutic Targets, Biological Activities, and Health Benefits. *Molecules*, **27**, Article 6474. https://doi.org/10.3390/molecules27196474

[61] Chen, Z., Sun, X., Li, X., Xu, Z., Yang, Y., Lin, Z., *et al.* (2020) Polydatin Attenuates Renal Fibrosis in Diabetic Mice through Regulating the Cx32-Nox4 Signaling Pathway. *Acta Pharmacologica Sinica*, **41**, 1587-1596. https://doi.org/10.1038/s41401-020-0475-6

[62] Reyna-Bolaños, I., Solís-García, E.P., Vargas-Vargas, M.A., Peña-Montes, D.J., Saavedra-Molina, A., Cortés-Rojo, C., *et al.* (2024) Polydatin Prevents Electron Transport Chain Dysfunction and ROS Overproduction Paralleled by an Improvement in Lipid Peroxidation and Cardiolipin Levels in Iron-Overloaded Rat Liver Mitochondria. *International Journal of Molecular Sciences*, **25**, Article 11104. https://doi.org/10.3390/ijms252011104

[63] Niu, X., Zhao, Y., Zhang, T., Sun, Y., Wei, Z., Fu, K., *et al.* (2023) Comprehensive Succinylome Analyses Reveal That Hyperthermia Upregulates Lysine Succinylation of Annexin A2 by Downregulating Sirtuin7 in Human Keratinocytes. *Journal of Translational Internal Medicine*, **12**, 424-436. https://doi.org/10.2478/jtim-2022-0061

[64] Ding, H., Tang, C., Wang, W., Pan, Y., Jiao, R. and Kong, L. (2022) Polydatin Ameliorates High Fructose-Induced Podocyte Oxidative Stress via Suppressing HIF-1*α*/NOX4 Pathway. *Pharmaceutics*, **14**, Article 2202. https://doi.org/10.3390/pharmaceutics14102202

[65] Ahn, B., Kim, H., Song, S., Lee, I.H., Liu, J., Vassilopoulos, A., *et al.* (2008) A Role for the Mitochondrial Deacetylase Sirt3 in Regulating Energy Homeostasis. *Proceedings of the National Academy of Sciences*, **105**, 14447-14452. https://doi.org/10.1073/pnas.0803790105

[66] Lin, L., Li, X., Li, Y., Lang, Z., Li, Y. and Zheng, J. (2024) Ginsenoside Rb1 Induces Hepatic Stellate Cell Ferroptosis to Alleviate Liver Fibrosis via the BECN1/SLC7A11 Axis. *Journal of Pharmaceutical Analysis*, **14**, Article 100902. https://doi.org/10.1016/j.jpha.2023.11.009

[67] Li, X., Cao, D., Sun, S. and Wang, Y. (2023) Anticancer Therapeutic Effect of Ginsenosides through Mediating Reactive Oxygen Species. *Frontiers in Pharmacology*, **14**, Article ID: 1215020. https://doi.org/10.3389/fphar.2023.1215020

[68] Jiang, L., Yin, X., Chen, Y., Chen, Y., Jiang, W., Zheng, H., *et al.* (2021) Proteomic Analysis Reveals Ginsenoside Rb1 Attenuates Myocardial Ischemia/Reperfusion Injury through Inhibiting ROS Production from Mitochondrial Complex I. *Theranostics*, **11**, 1703-1720. https://doi.org/10.7150/thno.43895

[69] Zhou, P., Xie, W., Luo, Y., Lu, S., Dai, Z., Wang, R., *et al.* (2018) Protective Effects of Total Saponins of Aralia Elata (Miq.) on Endothelial Cell Injury Induced by TNF-α via Modulation of the PI3K/Akt and NF-*κ*B Signalling Pathways. *International Journal of Molecular Sciences*, **20**, Article 36. https://doi.org/10.3390/ijms20010036

[70] He, J., Hong, Q., Chen, B., Cui, S., Liu, R., Cai, G., *et al.* (2022) Ginsenoside Rb1 Alleviates Diabetic Kidney Podocyte Injury by Inhibiting Aldose Reductase Activity. *Acta Pharmacologica Sinica*, **43**, 342-353. https://doi.org/10.1038/s41401-021-00788-0

[71] Ju, J., Li, J., Lin, Q. and Xu, H. (2018) Efficacy and Safety of Berberine for Dyslipidaemias: A Systematic Review and Meta-Analysis of Randomized Clinical Trials. *Phytomedicine*, **50**, 25-34. https://doi.org/10.1016/j.phymed.2018.09.212

[72] Wang, K., Yin, J., Chen, J., Ma, J., Si, H. and Xia, D. (2024) Inhibition of Inflammation by Berberine: Molecular Mechanism and Network Pharmacology Analysis. *Phytomedicine*, **128**, Article 155258. https://doi.org/10.1016/j.phymed.2023.155258

[73] Araj-Khodaei, M., Ayati, M.H., Azizi Zeinalhajlou, A., Novinbahador, T., Yousefi, M., Shiri, M., *et al.* (2023) Berberine-induced Glucagon-Like Peptide-1 and Its Mechanism for Controlling Type 2 Diabetes Mellitus: A Comprehensive Pathway Review. *Archives of Physiology and Biochemistry*, **130**, 678-685. https://doi.org/10.1080/13813455.2023.2258559

[74] Ni, W., Zhou, H., Ding, H. and Tang, L. (2020) Berberine Ameliorates Renal Impairment and Inhibits Podocyte Dysfunction by Targeting the Phosphatidylinositol 3-Kinase-Protein Kinase B Pathway in Diabetic Rats. *Journal of Diabetes Investigation*, **11**, 297-306. https://doi.org/10.1111/jdi.13119

[75] Turner, N., Li, J., Gosby, A., To, S.W.C., Cheng, Z., Miyoshi, H., *et al.* (2008) Berberine and Its More Biologically Available Derivative, Dihydroberberine, Inhibit Mitochondrial Respiratory Complex I: A Mechanism for the Action of Berberine to Activate AMP-Activated Protein Kinase and Improve Insu-Lin Action. *Diabetes*, **57**, 1414-1418.

https://doi.org/10.2337/db07-1552

[76] Qin, X., Jiang, M., Zhao, Y., Gong, J., Su, H., Yuan, F., *et al.* (2020) Berberine Protects against Diabetic Kidney Disease via Promoting PGC-1α-Regulated Mitochondrial Energy Homeostasis. *British Journal of Pharmacology*, **177**, 3646-3661. https://doi.org/10.1111/bph.14935

[77] Yang, L., Yuan, S., Wang, R., Guo, X., Xie, Y., Wei, W., *et al*. (2024) Exploring the Molecular Mechanism of Berberine for Treating Diabetic Nephropathy Based on Network Pharmacology. *International Immunopharmacology*, **126**, Article 111237. https://doi.org/10.1016/j.intimp.2023.111237

[78] Qin, X., Zhao, Y., Gong, J., Huang, W., Su, H., Yuan, F., *et al.* (2019) Berberine Protects Glomerular Podocytes via Inhibiting Drp1-Mediated Mitochondrial Fission and Dysfunction. *Theranostics*, **9**, 1698-1713. https://doi.org/10.7150/thno.30640